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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/859,503	05/18/2001	Marc J. McKennon	44033-122	5034

7590 01/02/2002

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EXAMINER	
BERCH, MARK L	
ART UNIT	**PAPER NUMBER**
1624	5

DATE MAILED: 01/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/859,503	MCKENNON ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-36 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-36 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 18-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The broken lines at the right side of the claim 1 formula are not defined.
2. Assuming that this means single or double bond, the lower of the three is impossible. The N already has three bonds to it. Making this bound double would give a N with four bonds and no charge, which is impossible.
3. Page 64, line 7, the choices of N-OH, sulfonyl and sulfinyl are all defective. These are divalent groups (e.g. sulfonyl is $-SO_2-$), but the R_1 variable itself is monovalent.
4. Likewise in line 8, phosphino and phosphinyl have more than one valence. What do these groups look like? Likewise, page 65, line 10.
5. Page 64, line 8, what is "sulfeno"? Likewise, page 65, line 9.
6. The term "acyl" is indefinite. Does this embrace acids of S? P? As? What does the stem look like, i.e. if the acyl is e.g. RC(O), what is R?

7. Page 64, line 14, first word, the term "thio" is a generic one, indicating the presence of sulfur in some form. As a substituent, it has no one single generally accepted meaning. There could be intended thioxo (=S) or mercapto (-SH). It can also denote replacement by S of some other atom (normally, oxygen or carbon) as in "thioalkoxy", where O is replaced by S. Perhaps some term which began with "thio", like thiophene was intended. Whatever choice is selected must be supported by the specification.
8. Page 64, line 8, "Phospho" is clearly in error. Phospho is a prefix denoting the presence of the element P in some form, e.g. phospholipid.
9. Page 64, line 11, in all 4 places, the C_1 is incorrect. Such things are impossible. A cycloalkyl ring cannot have one carbon. Likewise at line 20 and many other places.
10. "Heterocyclic" is indefinite. What is the size of the ring? What is the number and nature of the heteroatoms? Can the ring be fused or spiroconnected to another ring, and if so, what kind of ring? Can the ring be bridged? Unsaturated? Cf. *In re Wiggins*, 179 USPQ 421, 423.
11. Page 64, line 16, last choice is garbled. As written, it has an amino with three alkoxy groups and an amino attached, giving 5 bonds in all.
12. What is the purpose of the last choice of page 64, line 14? That is already covered by the last choice of line 18.
13. "Substituted" --- with what (at page 64, line 10, 19, etc).
14. Claim 34 says, "said disease", but claim 32 does not mention "disease".
15. "Amido" is indefinite. There is no way of knowing whether applicants intend just carboxylic acid amides, or whether sulfonic, phosphonic, etc amides are intended.

But even if carboxylic acid amido is intended, the term is undefined. Such a molecule generically has the formula RC(O)NR'R". One of the R choices will be used to attach, depending on whether the amido is C- or N-bound. Which end is intended for attachment? What is the nature of the other two R groups? Can the two of them together form a ring, and if so, of what type? The same problems exist for alkyl amido, but with one fewer undefined group. Thus, in RC(O)NR'R", one variable is alkyl, one is the bond, what is the third?

16. Some of the claim 6 terms are not heterocycles at all. For example, naphthylene and norbornane (line 23), pyrene (line 27), phenyl (line 26) are examples of this. The entire claim must be checked for this.
17. Page 64, lines 12 and 18 end with a period in the middle of the claim.
18. When a claim has more than alkyl in it, but just one range, does the range apply only to the first alkyl, or to both? See e.g. page 64, line 18, third and fourth choices, where there is an alkyl by itself, and one as part of the alkoxy.
19. Claim 3 is improperly dependent on claim 1. The haloalkyl and alkoxyalkyl choices are not provided for in claim 1. Nor is the methylphenyl choice provided for. This can be solved by adding these choices back into claim 1.
20. Likewise, claims 4-7 are improperly dependent on claim on claim 1. Note that claim 1 says e.g. alkyl and alkyl amino, not substituted alkyl and substituted alkyl amino.
21. What is the next to last term on claim 7? It appears to be a misspelling of the last term.
22. The next to last term on page 65 is not a carbocycle. Its an amide.

23. Claim 19 is garbled. It is written as a method for inhibiting, but the second (last) step is an analytical or diagnostic step.

24. In claim 19, line 1, the "or an activity mediated by cytokine" is of unclear function. All processes mediated by cytokines are cellular processes, and hence this is already covered by the material before the "or".

Claims 19-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The scope of "activity mediated by cytokine" cannot be deemed enabled. Is there any disease or normal body process that this would not embrace?

Cytokines are extraordinarily diverse in their structure and function. The term cytokine is used as a generic name for a diverse group of soluble proteins and peptides which act as humoral regulators and which, either under normal or pathological conditions, modulate the functional activities of individual cells and tissues. These proteins also mediate interactions between cells directly and regulate processes taking place in the extracellular environment. In general Cytokines act on a wider spectrum of target cells even than hormones and, unlike hormones, Cytokines are not produced by specialized cells which are organized in specialized glands, i.e. there is not a single organ source for these mediators. The fact that cytokines are secreted proteins also means that the sites of their expression does not necessarily predict the sites at which they exert their biological function.

As for structure, most Cytokines are unrelated in terms of sequence.

Almost all Cytokines are pleiotropic effectors showing multiple biological activities. In addition, multiple cytokines often have overlapping activities and a single cell frequently interacts with multiple cytokines with seemingly identical responses (cross-talk). One of the consequences of this functional overlap is the observation that one factor may frequently functionally replace another factor altogether or at least partially compensate for the lack of another factor. Since most Cytokines have ubiquitous biological activities, their physiologic significance as normal regulators of physiology is often difficult to assess.

The activities of cytokines as a group are extremely complex. Many Cytokines show stimulating or inhibitory activities and may synergize or antagonize also the actions of other factors. A single cytokine may elicit reactions also under certain circumstances which are the reverse of those shown under other circumstances. The type, the duration, and also the extent of cellular activities induced by a particular cytokine can be influenced considerably by the micro-environment of a cell, depending, for example, on the growth state of the cells (sparse or confluent), the type of neighboring cells, cytokine concentrations, the combination of other Cytokines present at the same time, and even on the temporal sequence of several Cytokines acting on the same cell. The responses elicited by Cytokines are therefore contextual and the "informational content", i.e. the intrinsic activities of a given cytokine may vary with conditions.

Some attempts have been made to organize cytokines along lines of function, which show the tremendous variety of what is covered by "cytokine". For example, one category is chemokines, a generic name given to a family of pro-inflammatory

activation-inducible Cytokines. These include a) SIS family such as SIS-alpha, SIS-gamma and SIS-epsilon, b) SIG family including JE, KC, MGSA (melanoma growth stimulatory activity), PF4 (platelet factor-4), PBP (platelet basic protein), LDCF (lymphocyte-derived chemotactic factor), RANTES, and SMC-CF, c) SCY family including SCY A1, SCY A2, SCY A3, SCY A4, SCY A5, SCY A6, SCY A7, SCY A8, SCY A9, SCY A10, SCY A11, SCY A12, SCYA13, SCY A14, SCY A15, SCY A16, SCY A17, SCY A18, SCY A19, SCY A20, SCY A21, SCY A22, SCY A23, SCY A24, SCY A25,SCY A26 and many others as well.

Another category is Motogenic cytokines, a category Cytokines that influence the motility and migration of cells in ways other than affected by chemotactic processes. The collective term is an functional definition and there is no structural basis that would allow different factors to be classified as motogenic cytokines. Examples include AAMP (Angio-associated migratory cell protein), Adrenomedullin, AMF (autocrine motility factor), ATX (autotaxin), B16-F1 melanoma autocrine motility factor, DF (dissociation factor), Epitaxin, FDMF (fibroblast-derived motility factor), FMSF [fibroblast motility-stimulating factor] ISF (invasion stimulating factor), Ladsin, Monocyte-derived scattering factor, MSF (migration stimulating factor), PDMF (pancreatic cancer-derived motility factor), SF (scatter factor), SFL (scatter factor-like), and Vitronectin.

Another category is the B-cell growth factor (BCGF), which includes CD23, IL1, IL2, IL4, IL5, IL6, IFN-gamma, TNF-alpha and TNF-beta.

Another type are the colony stimulating factors, which regulate white blood cell production and orchestrate the control of the growth and differentiation of bone marrow progenitor cells. These include M-CSF (macrophage-specific), G-CSF (granulocyte-

specific), GM-CSF (macrophage/granulocyte-specific), IL3 (multifunctional), IL-7 and Stem Cell Factor (SCF) and MEG-CSA (megakaryocyte-specific).

A large category of cytokines is the angiogenisis factors, which include aFGF, ANF, Angiogenin, Angiotropin, AtT20-ECGF, B61, bFGF, CAM-RF, ChDI, CLAF, ECGF, ECI, EDMF, EGF, EMAP, Neurothelin, Endostatin, Endothelial cell growth inhibitor, Endothelial cell-viability maintaining factor, Epo, FGF-5, IGF-2, HBNF, HGF, HUAF, IFN-gamma, IL1, K-FGF, LIF, MD-ECI, MECIF, Oncostatin M, PD-ECGF, PDGF, PF4, PlGF, Prolactin, TNF-alpha, TNF-beta, Transferrin, VEGF, and others.

There are many, many other cytokines, including IL10, IL12, IL9, IP-10, GRO, and 9E3.

In view of the considerable diversity of structure and function, the idea that a single compound, let alone a genus of millions, could affect cytokines, or activities regulated by cytokines, generally is contrary to what is known about these. No such compound has ever been found, and given what is already known about the diversity of such gents, thee is no reason to think a compound could act generally against cytokines.

The other branch of claim 19, "inhibiting a cellular process" That reads essentially on treatment of all disease, since all disease involves a cellular process. Moreover, the idea that a compound could inhibit cellular processes generally is absurd. In addition, the term "inhibiting a cellular process" also covers inhibiting normal and needed processes. The specification does not teach what the point is of inhibiting processes which are essential for life. That is, this language calls for inhibiting both desired and undesired processes.

Claim 36 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment, does not reasonably provide enablement for prevention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Preventing a person from having NIDDM in the first place is beyond the scope of medicine.

Claims 10, 11, 14, 15 and 17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. These compounds do not fall within the scope of the page 8 formula, to which the utility is attached. Note that R4, even if H, is required to be present. The species of these claims are not tautomers of the page 8 formula.

Claims 1-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for most aspects, does not reasonably provide enablement for solvates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

There are many examples. But the numerous examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds

exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." Hence, applicants must show that solvates can be made, or limit the claims accordingly.

Specification

The abstract is objected to; it needs the formula and definitions for R2 and R3.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 703-308-4718. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 308-4716. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 708-308-1235.

Mark L. Berch
Primary Examiner
Art Unit 1624

December 21, 2001